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Out of Hospital Cardiac Arrest Survivors with Inconclusive Coronary Angiogram: Impact of Cardiovascular Magnetic Resonance on Clinical Management and Decision-Making

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27 **Abstract**

28 **Background** Non-traumatic out of hospital cardiac arrest (OHCA) is the leading cause of death
29 worldwide, mainly due to acute coronary syndromes. Urgent coronary angiography with view to
30 revascularisation is recommended in patients with suspected acute coronary syndrome. Diagnosis
31 and management of patients with inconclusive coronary angiogram (unobstructed coronaries or
32 unidentified culprit lesion) is challenging. We sought to assess the role of Cardiovascular Magnetic
33 Resonance (CMR) in the diagnosis and management of OHCA survivors with an inconclusive
34 coronary angiogram.

35 **Methods and Results** This is a retrospective multicentre CMR registry analysis of OHCA
36 survivors with an inconclusive angiogram. Clinical, ECG and multi-modality imaging data were
37 analysed. Clinical impact of CMR was defined as a change in diagnosis or management. Out of 174
38 OHCA survivors referred for CMR, 110 patients (63%, 84 male, median age 58) had an
39 inconclusive angiogram. CMR identified a pathologic substrate in 76/110 patients (69%): ischemic
40 heart disease was found in 45 (41%) and non-ischemic heart disease in 31 (28%). A structurally
41 normal heart was found in 25 patients (23%) and non-specific findings in 9 (8%). As compared to
42 trans-thoracic echocardiogram, CMR proved to be superior in identifying a pathologic substrate
43 (69% vs 54%, $p=0.018$). The CMR study carried a clinical impact in 70% of patients, determining a
44 change in diagnosis in 25%, in management in 29% and a change in both in 16%.

45 **Conclusions** CMR showed a promising role in the diagnostic work-up of OHCA survivors with
46 inconclusive angiogram and its wider use should be considered.

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53 **Introduction**

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55 Non-traumatic out of hospital cardiac arrest (OHCA) is the leading cause of death worldwide (1-3)
56 with an estimated incidence of 0.5/1000 person year (4-8). Acute coronary syndromes (ACS)
57 account for more than 2/3 of cases (9-12). According to AHA guidelines, urgent angiography with
58 view to primary percutaneous coronary intervention is a class IB recommendation in patients with
59 resuscitated cardiac arrest whose electrocardiogram (ECG) shows ST elevation (STE) myocardial
60 infarction (MI) (13). Given the high incidence of underlying coronary artery disease (CAD) in this
61 group of patients, European guidelines extended the recommendation to incorporate patients
62 without diagnostic STE, but with high suspicion of on-going infarction (class IIaB) (14). However
63 non-ischemic cardiomyopathy accounts for up to 15% of OHCA (15-19) and a structurally normal
64 heart can be found in up to 10-20% of cases (20-23). While evidence of culprit lesion on angiogram
65 supports acute ischemia as the cause of OHCA, diagnosis and clinical management of OHCA
66 survivors with inconclusive coronary angiogram (either non-identifiable culprit lesion or
67 unobstructed coronary arteries) is challenging. Cardiovascular magnetic resonance (CMR) is a non-
68 invasive imaging technique providing accurate diagnosis based on its superior spatial resolution and
69 unique non-invasive tissue characterization.

70 We sought to assess the additional role and clinical impact of CMR in the diagnosis and
71 management of OHCA survivors with an inconclusive coronary angiogram.

72

73 **Materials and Methods**

74 The CMR registries from two tertiary Cardiac centres (Bristol, South West of England and Padua,
75 Veneto Region, Italy) were analysed to identify OHCA survivors who underwent urgent coronary
76 angiogram followed by CMR (October 2009-November 2015). The study focused on the analysis of
77 patients with an “inconclusive angiogram”, defined as evidence of stable obstructive CAD (SCAD)
78 with no culprit lesion or unobstructed coronaries (normal coronaries/non-obstructive CAD). Culprit

79 lesion was defined as obstructive ($\geq 70\%$) CAD with TIMI 0/1 flow with abrupt closure, or TIMI
80 2/3 flow with features suggestive of thrombus/ulcerated plaques, ST segment- T wave changes in
81 the corresponding ECG location, and evidence of matching regional wall motion abnormality on
82 left ventriculogram or echocardiogram (24).

83

84 CMR

85 CMR was performed on a 1.5T scanner (Avanto, Siemens Healthcare, Germany) with a protocol
86 including long and short axis cine sequences and post-contrast imaging, performed ten minutes after
87 intravenous administration of 0.1 mmol/Kg of Gadobutrol (Gadovist 1.0 mmol/ml, Bayer-Schering,
88 Berlin, Germany) in identical planes to cine images. Additional sequences for the assessment of
89 myocardial oedema (T2-short tau inversion recovery, T2-STIR) or myocardial ischemia (stress
90 perfusion with 140 to 210 ug/Kg/min adenosine) were performed when indicated, based on clinical
91 and angiographic findings. Ventricular function was assessed with dedicated software (Circle
92 Cardiovascular Imaging, Calgary, Canada), by tracing endo- and epicardial borders on each short
93 axis cine slice in end-diastole and end-systole. All volumes were indexed to body surface area. The
94 localization, extent and distribution pattern of late gadolinium enhancement (LGE) were assessed
95 by using short- and long-axis views and confirmed only if detectable in two orthogonal planes. The
96 pattern of LGE distribution was defined as ischemic, subendocardial or transmural, if involving
97 $< 50\%$ or $\geq 50\%$ of wall thickness, respectively, and as mid-wall/epicardial if patchy/spotty intra-
98 mural or sub-epicardial enhancement was detected. The presence of LGE at the right ventricle/left
99 ventricle insertion points, in the absence of other distribution patterns, was defined as non-specific
100 findings, as its diagnostic and prognostic meaning is still unclear.

101 All the analyses were carried out in accordance with the recommendation of the Society for
102 Cardiovascular Magnetic Resonance (25). The study was reviewed by the local Institutional
103 Research and Innovation Department and in view of the retrospective design, formal ethical
104 approval was waived off. All patients gave written informed consent.

105

106 Clinical impact

107 Clinical, ECG and echocardiographic data were collected and independently analysed by two
108 clinicians blinded to CMR findings. A diagnosis was made based on clinical and imaging data
109 available prior to CMR. According to previously used definitions (26), “clinical impact” of CMR
110 was defined as change in diagnosis, compared to the composite pre-CMR diagnosis, or change in
111 management. A change in management was defined as CMR findings either leading to change in
112 medication, to an invasive procedure (i.e. repeat angiogram, myocardial revascularization, ICD
113 implantation) or to the avoidance of such invasive procedures. Patients with a change both in
114 diagnosis and management were only counted once.

115

116 **Statistical Analysis**

117 Continuous and categorical variables are expressed as mean±SD or median (IQR), and n (%),
118 respectively. Categorical variables were compared by using the chi-square or Fisher exact test, as
119 appropriate. Continuous data were compared by using the 2-tailed unpaired t test (for normally
120 distributed data sets) or by using the Mann-Whitney U test. Inter-rater agreement for categorical
121 variables was assessed by Cohen’s kappa coefficient. A p-value of <0.05 was considered
122 statistically significant. Data were analysed with SPSS® version 23 (IBM®).

123

124 **Results**

125 **Clinical characteristics**

126 Out of 174 consecutive OHCA survivors referred to CMR after coronary angiogram (performed on
127 same day of admission, IQR 0-2 days), 110 patients (63%, 84 male, age 58 years, IQR 46-68) had
128 an inconclusive angiogram and were enrolled in the study: 37 patients (34%) had evidence of
129 SCAD with no culprit lesion and 73 patients (66%) showed unobstructed coronaries. The first
130 registered rhythm was ventricular tachycardia (VT)/ventricular fibrillation (VF) in 104 patients

131 (95%) and pulseless electrical activity (PEA) in 6 patients (5%). The first ECG was available in 86
132 patients (78%): non-ST elevation (non-STE) was reported in 68 patients (79%), STE in 18 (21%).
133 SCAD patients with no culprit lesion were more frequently men ($p=0.006$) and significantly older
134 compared to patients with unobstructed coronaries ($p<0.001$); risk factors were similar, except for
135 hypertension ($p=0.001$) and known CAD ($p<0.001$), which were more frequent among SCAD
136 patients with no culprit lesion. STE was more common among SCAD patients with no culprit
137 ($p=0.002$). Patients' characteristics are listed in **Table 1**.

138

139 **CMR findings**

140 Among patients with inconclusive angiogram, CMR was performed within 2 weeks from the index
141 event (median 1.4 weeks, IQR 0.9-2.4, no difference between centres, $p=0.588$). Time to CMR was
142 significantly shorter among patients with inconclusive angiogram, as compared to patients found to
143 have an acute coronary event on angiogram ($p=0.001$). Median left ventricular ejection fraction
144 (LVEF) was 57% (IQR 44-64), median indexed left ventricular end-diastolic volume (LVIEDV)
145 and end-systolic volume (LVIESV) was 87 ml/m² (IQR 73-110) and 38 ml/m² (IQR 27-56),
146 respectively. LVEF was significantly higher among patients with unobstructed coronaries (p
147 <0.001). Wall motion abnormality was reported in 55 patients (50%), with regional or diffuse
148 pattern in 38 (35%) and 17 patients (15%), respectively (**Table 2**).

149 On post-contrast sequences LGE was found in 72/110 patients (65%), and it was significantly more
150 common among SCAD patients with no culprit lesion (33/37 vs 39/73, $p<0.001$). Analysis of LGE
151 distribution pattern showed subendocardial LGE in 15 patients (14%), mid-wall/epicardial in 26
152 patients (24%), and transmural LGE in 27 patients (25%). More than one distribution pattern was
153 reported in 4 patients (3%). No LGE was found in 38 patients (34%). T2-STIR sequences for
154 myocardial oedema were performed in 58 patients (53%), more frequently in patients with
155 unobstructed coronaries ($p=0.001$); myocardial oedema was found in 18 patients (31%). Presence of
156 myocardial oedema was not significantly associated with the timing of CMR; however, there was a

157 trend towards a higher prevalence of myocardial oedema among patients undergoing CMR within
158 one week from index event ($p=0.064$). There was no difference in prevalence of myocardial
159 oedema between the two groups.

160 Overall, CMR identified a pathologic substrate in 69% of the population: IHD was the final
161 diagnosis in 45 patients (41%) and non-ischemic heart disease (NIHD) in 31 (28%). Non-specific
162 findings were found in 9 patients (8%) and a structurally normal heart in 25 (23%)(**Table 3**). CMR
163 findings between the two subgroups differed significantly ($p<0.001$)(**Figure 1 and Supplementary**
164 **File 1**)

165

166 **Stable obstructive CAD with no culprit lesion**

167 Thirty-four patients (92%) were found to have IHD, a structurally normal heart (no myocardial
168 oedema, late enhancement or inducible ischemia) was found in 3 (8%). On T2-STIR sequences,
169 performed in 11 patients (30%), myocardial oedema was found in a single coronary artery territory
170 in 5 (45%), helping to localise the culprit lesion. Stress perfusion CMR was performed in 15
171 patients (41%): inducible ischemia was reported in 10 patients (67%) (single coronary artery
172 territory in 7 patients and multi-vessel territory in 3), 90% of whom received percutaneous/surgical
173 revascularization. A viability study was performed in the remaining 22 (59%) to guide treatment
174 (revascularization/ optimization of medical therapy); CMR showed findings consistent with viable
175 myocardium in 15 patients (68%), of which 12 (80%) underwent revascularization.

176

177 **Unobstructed coronaries**

178 IHD was diagnosed in 11 patients (15%) and NIHD in 31 (43%), with myocarditis (23%) and DCM
179 (10%) being the most common, followed by congenital and acquired cardiomyopathies (**Table 3**).
180 A structurally normal heart was found in 22 patients (30%) and non-specific findings in 9
181 (12%)(**Figure 2**). On T2-STIR sequences, performed in 64% of patients, the presence of

182 myocardial oedema in 13 (28%) identified an acute, reversible, cause of OHCA in 3 IHD patients
183 and in those diagnosed with myocarditis and TTC. LGE was found in 53%.

184

185 **Comparison between CMR and trans-thoracic echocardiogram**

186 A trans-thoracic echocardiogram (TTE) performed within 1 week from CMR was available in 92
187 patients (84%). Median LVEF by TTE was lower compared to CMR (50% vs 57%, $p < 0.001$). TTE
188 identified a pathologic substrate in 50/92 patients (54% vs 69% by CMR, $p = 0.018$): the final
189 diagnosis was IHD in 26/92 patients (28%) and NIHD in 24/92 patients (26%). A structurally
190 normal heart was found in 20/92 patients (22%) and non-specific findings (structural and functional
191 abnormalities not attributable to a conclusive diagnosis) in 22 (24%). CMR and TTE provided the
192 same diagnosis in 51/92 patients (55%)(**Table 4**). There was a moderate agreement between CMR
193 and TTE with regards to IHD, which was confirmed on CMR in 22/26 patients (85%)(Cohen's
194 kappa 0.50), and to structurally normal heart, confirmed on CMR in 11/20 patients (55%)(Cohen's
195 kappa 0.43). There was a fair agreement with regards to NIHD, which was confirmed on CMR in
196 15/24 patients (63%)(Cohen's kappa 0.21); based on tissue characterization CMR identified 7
197 patients with an ischemic distribution pattern of LGE. CMR provided a diagnosis in 14/22 (64%)
198 patients with non-specific findings on TTE, identifying 6 patients with IHD and 8 patients with
199 NIHD. The ability of CMR to be more definite regarding the underlying cardiac abnormalities was
200 mainly based on LGE.

201

202 **Clinical impact of CMR**

203 CMR provided a clinical impact in 77/110 patients (70%), leading to change in diagnosis in 27
204 patients (25%), in management in 32 (29%), and both in diagnosis and management in 18 patients
205 (16%). An entirely new diagnosis was found in 25% of patients, most commonly structurally
206 normal heart (11%) and NIHD (10%). CMR led to an invasive procedure in 32 (29%) patients,
207 namely myocardial revascularization in 21 (19%) and ICD implantation in 11 (10%). Based on

208 CMR findings, an invasive procedure was avoided in 15 (14%) patients. CMR had greater clinical
209 impact in SCAD patients with no culprit lesion ($p=0.002$), more frequently experiencing a change
210 in management (86% vs. 25% unobstructed coronaries, $p < 0.001$); a change in diagnosis occurred
211 more frequently among patients with unobstructed coronaries (58% vs. 8% SCAD patients, p
212 < 0.001).

213

214 **Discussion**

215 The main findings of our study were that: 1) 2/3 of OHCA survivors referred to CMR have
216 inconclusive findings on angiogram; 2) CMR identified a pathologic substrate in 69% of the
217 population and a structurally normal heart in 23%; 3) CMR had a clinical impact in more than two
218 thirds of patients.

219

220 Acute coronary syndromes account for more than two thirds of OHCA (9-12) mainly secondary to
221 acute coronary thrombosis (26) or ruptured plaque (27), as confirmed by autopsy series.

222 International guidelines recommend urgent angiography in OHCA survivors with STE (13, 14) or
223 whenever there is high suspicion of on-going infarction, irrespective of ECG (14). However, only a
224 minority of cases (30-40%) shows angiographic and clinical evidence of ACS (27), a figure similar
225 to that (37%) in our study. Causes other than acute ischemia are reported in up to 30% of cases (28).

226 When acute ischemia is the obvious cause of OHCA, fewer patients are referred to CMR, mainly to
227 assess the extent of myocardial scarring and the functional significance of bystander CAD. On the
228 other hand, an inconclusive angiogram poses a diagnostic dilemma requiring further investigation,
229 and to our knowledge this is the first study looking at the role and clinical impact of CMR in OHCA
230 survivors with this angiographic finding. Identifying OHCA aetiology is often challenging in the
231 acute setting, as clinical data are often lacking and ECG and echocardiographic interpretation might
232 be affected by resuscitation manoeuvres or external defibrillation (27, 29). However, correct
233 identification of the underlying cause, especially if reversible, plays a determinant role for

appropriate treatment strategy and long-term prognosis. CMR has a well-established diagnostic role, both in the ischemic and non-ischemic scenario, based on its superior tissue characterization properties. In our study, CMR could identify an underlying pathologic substrate in 69% of the population, as compared to 54% by TTE ($p=0.018$), and this was mainly due to LGE analysis. This superior diagnostic ability carried additional value and clinical impact over TEE in the management of these patients; for example, non-specific findings were more frequently reported by TTE (24% vs 8%), but CMR was able to identify a pathologic substrate in two thirds of them. We found a high prevalence of LGE among OHCA survivors (65%), in keeping with that recently reported by Neilan (71%) in OHCA survivors referred to CMR because of an unclear diagnosis (after clinical and diagnostic assessment) (30). The aim of their study was to identify the role of LGE as an arrhythmic substrate and as a predictor of adverse cardiovascular events. They found that LGE presence and extent are the strongest predictors of adverse arrhythmic outcome, further confirming the relationship between myocardial damage and major arrhythmias, and strengthening the association between tissue characterization and arrhythmic risk, independent of the ejection fraction, as reported by many studies on cardiovascular outcome (31-35). White et al. (36) showed that CMR-based imaging had a pick-up diagnostic rate of 74% in identifying the myocardial substrate of ventricular arrhythmias vs. 51% based on non-CMR imaging (i.e. diagnosis of MI missed in one third of patients on non-CMR imaging). In our study, CMR identified ischemic myocardial damage in 11 patients (15%) with unobstructed coronaries on angiogram; TTE diagnosed IHD in only one of them. Among 88 patients with no label of prior MI, Neilan (30) found ischemic LGE in 49, thus supporting the hypothesis that the presence of LGE in patients with unobstructed coronaries identifies a subgroup of patients at increased risk of arrhythmic events. Compared to Neilan, our study explored the comparative value of CMR vs TTE, as well as the clinical impact of CMR in this patients' cohort.

As already confirmed in different populations, such as in heart failure (26), we found that CMR changed both diagnosis and management in a considerable proportion of OHCA survivors (70%).

260 Of interest, CMR showed a clinical impact both in patients with unobstructed coronaries, mainly by
261 providing a change in diagnosis, and in SCAD patients with no culprit lesion, mainly by a change in
262 management. An entirely new diagnosis was identified in 25% of cases, mainly based on tissue
263 characterization: a structurally normal heart was found in 11% of patients, based on the absence of
264 LGE, and NIHD was diagnosed in 10%. Stress perfusion CMR has a well-established role not only
265 in detecting CAD and guiding subsequent treatment strategy (37-39), but also in the identification
266 of patients at increased risk of major adverse cardiovascular events (40, 41). Stress perfusion CMR,
267 performed in nearly half of SCAD patients with no culprit lesion, found inducible ischemia in 67%
268 of patients, guiding myocardial revascularization in nearly all of them. It is well-established that
269 CMR has a role, over and above TTE, in re-classifying patients with regards to primary prevention
270 ICD eligibility based on LVEF criteria (42), as it is the gold standard for LV function (43). The
271 ability of CMR to detect reversible myocardial damage could play a role in guiding secondary
272 prevention ICD implantation. In our patient population of OHCA survivors, CMR identified acute
273 reversible myocardial injury (acute myocarditis and acute ischemia), thus avoiding secondary ICD
274 implantation, as per guidelines, in 6% of patients.

275

276 **Limitations**

277 The main limitation of this study is the retrospective design. However, conducting a prospective
278 trial in OHCA survivors might be difficult due to high mortality rate, variable downtime and
279 consent. Sequences for myocardial oedema were available for analysis in half of the population,
280 thus the clinical impact of oedema analysis might have been higher if performed in all patients. A
281 structurally "normal" heart by TTE and CMR reflects the absence of gross ischemic or non-
282 ischemic underlying conditions, but it cannot exclude ultra-structural abnormalities. Although
283 endomyocardial biopsy is the gold standard to assess myocardial abnormalities, it is an invasive
284 technique, not widely performed clinically and not performed in our patients; therefore some more
285 subtle histological and cellular abnormalities cannot be excluded. With all the above limitations,

286 this is a real world study that reflects clinical practice in most centres. Our study only analysed the
287 presence of focal fibrosis, although it is increasingly evident that the presence of diffuse fibrosis has
288 a prognostic role, detecting patients at higher risk of fatal arrhythmias (44). The use of the most
289 recent T1 mapping technique might help further understand the pathologic substrate in this group of
290 patients.

291

292 **Conclusions**

293 Although ACS account for the majority of OHCA, 63% of the survivors in our cohort had an
294 inconclusive angiogram. CMR proved to be superior to TEE in the identification of a pathologic
295 substrate for the event in this cohort (69% vs 54%, $p=0.018$) and its findings had a clinical impact
296 in 70% of patients, providing a significant change both in diagnosis and in management. CMR
297 showed a promising role in the clinical and diagnostic work-up of OHCA survivors with
298 inconclusive angiogram and its wider use should be considered. Further prospective studies are
299 warranted to confirm these results in a larger population.

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312 **Disclosures**

313 Dr Bucciarelli-Ducci is Consultant for Circle Cardiovascular Imaging.

314 There is no relationship to industry to declare.

315

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507 **Figure Legends**

508 **Figure 1. CMR findings in OHCA survivors with inconclusive angiogram**

509 Final CMR findings, according to coronary angiogram data, in OHCA survivors with inconclusive
510 angiogram. Boxes in bold show the final CMR findings in the overall cohort of OHCA survivors
511 with inconclusive angiogram. SCAD, stable coronary artery disease.

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513 **Figure 2. CMR findings.**

514 Post-contrast 3 chamber long-axis view showing transmural myocardial infarction (A). Post-
515 contrast 3 chamber long-axis view of a patient with hypertrophic cardiomyopathy (HCM) and
516 replacement fibrosis of the hypertrophied septum (B, arrow). Post-contrast 4 chamber long axis
517 view of a patient with biventricular arrhythmogenic right ventricular cardiomyopathy (ARVC) (C).
518 3 chamber long axis cine showing prolapse of the posterior mitral leaflet at end-systole (D). Post-
519 contrast short axis view showing epicardial enhancement of the basal lateral wall in a patient with
520 healed myocarditis (E, arrow). Post-contrast short axis view showing non- specific late
521 enhancement of the inferior insertion point (F, arrow).

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533 **Supplementary Material**

534 **Supplementary File 1. CMR findings according to coronary angiogram results**

535 Top panel, no culprit lesion identified on angiogram: ischemic heart disease (IHD) was the most
536 common diagnosis, although CMR identified a structurally normal heart in 8% of patients. Bottom
537 panel, unobstructed coronary arteries: non-ischemic heart disease (NIHD) and structurally normal
538 heart were the most common findings, but CMR identified an ischemic cardiomyopathy in 15% of
539 patients.

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